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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/730,469	12/04/2000	Anthony P. Heaney	CEDAR-45257	7071

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EXAMINER	
CHEN, SHIN LIN	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/730,469	Applicant(s) Heaney et al.
	Examiner Shin-Lin Chen	Art Unit 1633

-- Th MAILING DATE of this communication appears on the cover sh et with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 9, 10, 14, 15, 17-23, 42, 43, 46, and 47* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7, 9, 10, 14, 15, 17-23, 42, 43, 46, and 47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4 and 9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of groups I, claims 1-7, 9-23, 42, 43, 46 and 47, in Paper No. 12 is acknowledged.

2. Claims 8, 24-41, 44, 45, 48 and 49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 12.

Applicants' amendment filed 8-13-02 has been entered. Claims 8, 11-13, 16, 24-41, 44, 45, 48 and 49 have been canceled. Claims 1, 9, 14, 15, 46 and 47 have been amended. Claims 1-7, 9, 10, 14, 15, 17-23, 42, 43, 46 and 47 are pending and under consideration.

Priority

3. If applicant desires priority under 35 U.S.C. 120 or 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the **first sentence** of the specification following the title, preferably as a separate paragraph. The reference regarding the claimed priority is in the second paragraph rather than appears as the first sentence (see specification, p. 1, lines 9-14). Appropriate correction is required.

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the provisional application 60/031,338 and applications 08/894,251 and PCT/US97/21463 fail to disclose the nucleotide sequence of SEQ ID No. 10 and the amino acid sequence of SEQ ID No. 9, and fail to disclose the PTTG-C function that downregulates PTTG expression. Thus, the benefits of the provisional application 60/031,338 and applications 08/894,251 and PCT/US97/21463 have been denied. The effective filing date of the present application is 5-12-00.

Double Patenting

5. Claims 1-7, 9, 10, 14, 15 and 17-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9, 10, 14, 15 and 17-23 of copending Application No. 09/569,956 ('956). Although the conflicting claims are not identical, they are not patentably distinct from each other because although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 1-7, 9, 10, 14, 15 and 17-23 of the present application are directed to a method of inhibiting neoplastic cellular proliferation or transformation of a mammalian **breast or ovarian** cell that overexpresses PTTG by using a composition or an expression vector comprising a PTTG-C polynucleotide encoding a PTTG-C peptide having the amino acid sequence consisting of SEQ ID No. 9 or a peptide fragment thereof comprising at least 15 contiguous amino acid

residues including a proline-rich region of SEQ ID No. 9 so as to down regulate endogenous PTTG expression or PTTG function.

Claims 1-7, 9, 10, 14, 15 and 17-23 of the '956 are directed to a method of inhibiting neoplastic cellular proliferation or transformation of a **mammalian cell** that overexpresses PTTG by using a composition or an expression vector comprising a PTTG-C polynucleotide encoding a PTTG-C peptide having the amino acid sequence consisting of SEQ ID No. 9 or a peptide fragment thereof comprising at least 15 contiguous amino acid residues including a proline-rich region of SEQ ID No. 9 so as to down regulate endogenous PTTG expression or PTTG function.

The mammalian cell of '956 encompasses breast and ovarian cell, and it would have been obvious for one of ordinary skill at the time of the invention to inhibit neoplastic cellular proliferation or transformation of a mammalian **breast or ovarian** cell that overexpresses PTTG according to the teaching of '956.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

6. Claims 1, 15, 17, 18 objected to because of the following informalities: The term "and/or" in claims 1, 15, 17 and 18 is improper. Changing the term "and/or" to "...or...or both" would be remedial. Appropriate correction is required.

7. Claims 14 and 15 are objected to because of the following informalities: The parenthesis "( )" in line 3 of claim 14 and lines 8-9 of claim 15 are unnecessary and should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "DNA analog" in claim 7 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what is considered "DNA analog"? The specification fails to specifically define the phrase "DNA analog". Claim 10 depends on claim 7 but fails to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 7, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7, 9 and 10 are directed to a polynucleotide that is a DNA analog or a peptide nucleic acid, and a method of using said polynucleotide.

The specification fails to provide an enabling disclosure that a DNA analog or a peptide nucleic acid can be replicated and transcribed by DNA polymerase and RNA polymerase, respectively, and that they can encode peptide sequences.

As discussed in the 112 second paragraph rejection, it is unclear as to the metes and bounds of what is considered "DNA analog", and a RNA or a DNA with phosphorothiate linkage are considered DNA analogs. However, RNA and phosphorothioated DNA can not be replicated and transcribed by DNA polymerase and RNA polymerase, respectively, and they can not encode peptide sequences.

Claim 9 is directed to a method of using a polynucleotide that is a peptide nucleic acid. A peptide nucleic acid has polypeptide backbone having its side chains of amino acid residues replaced with purine or pyrimidine of nucleic acids. Thus, a peptide nucleic acid itself is a peptide or polypeptide but not a polynucleotide, and a peptide nucleic acid can not be replicated and transcribed by DNA polymerase and RNA polymerase, respectively, and it can not encode any peptide sequence. One skilled in the art at the time of the invention would not know how to

use the claimed DNA analogs and peptide nucleic acid to encode a peptide sequence and would require undue experimentation to practice over the full scope of the invention claimed.

12. Claims 1-7, 9, 10, 14, 15, 17-21, 23, 42, 43, 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting proliferation of breast carcinoma cells by injecting MCF-7 breast carcinoma cells transfected with expression vector expressing PTTG-C peptide into nude mice, does not reasonably provide enablement for a method of inhibiting neoplastic cellular proliferation or transformation of a mammalian breast or ovarian cell that overexpresses PTTG by delivering a composition comprising a naked polynucleotide encoding a PTTG-C peptide without any expression vector to said cell via any administration route *in vivo*, or by delivering any expression vector comprising a polynucleotide encoding a PTTG-C peptide to said cell via administration route other than direct *in situ* administration *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-7, 9, 10, 14, 15, 17-21, 23, 42, 43, 46 and 47 are directed to a method of inhibiting neoplastic cellular proliferation or transformation of a mammalian, such as human, breast or ovarian cell that overexpresses PTTG by delivering a composition or an expression vector comprising a PTTG-C polynucleotide encoding a PTTG-C peptide having the amino acid sequence consisting of SEQ ID No. 9 or a peptide fragment thereof comprising at least 15

contiguous amino acid residues including a proline-rich region of SEQ ID No. 9 to a mammalian breast or ovarian cell so as to down regulate endogenous PTTG expression or PTTG function. Claim 7 specifies the polynucleotide is a DNA or DNA analog. Claim 9 specifies the polynucleotide is a peptide nucleic acid. Claims 17 and 18 specify the polynucleotide further comprises a second DNA segment encoding an uptake-enhancing or importation-competent peptide segment. Claims 42, 43, 46 and 47 specify further administering a cytotoxic chemotherapeutic agent to the mammalian breast or ovarian cell.

The specification discloses inhibition of neoplastic proliferation of breast carcinoma cells by injecting MCF-7 breast carcinoma cells transfected with expression vector expressing PTTG-C peptide into athymic nude mice (specification, p. 74-75). The claims encompass inhibiting neoplastic proliferation or transformation of mammalian breast or ovarian cell growth with a composition comprising a polynucleotide encoding the amino acid sequence of SEQ ID No. 9 or its fragment containing the proline-rich region, or with any expression vector expressing the amino acid sequence of SEQ ID No. 9 or its fragment containing the proline-rich region via any administration route *in vivo*.

The specification fails to provide adequate guidance and evidence that a composition comprising the polynucleotide set forth above without any expression vector or promoter/enhancer operably linked to said polynucleotide can inhibit neoplastic cellular proliferation or transformation of a mammalian breast or ovarian cell *in vivo* via any administration route. It was well known in the art that a promoter/enhancer is required for the

expression of a gene product, such as a protein or a peptide. There is no evidence of record that a polynucleotide without promoter/enhancer or expression vector can be expressed in a cell *in vitro* or *in vivo*. Thus, one skilled in the art at the time of the invention would not know how to use the claimed composition comprising the polynucleotide set forth above to inhibit neoplastic cellular proliferation or transformation *in vitro* or *in vivo*, and would require undue experimentation to practice over the full scope of the invention claimed.

Further, claim 14 reads on using a polynucleotide having the nucleotide sequence consisting of a sequence complementary to SEQ ID No. 10 or complementary to a degenerate coding sequence of SEQ ID No. 10 to inhibit neoplastic proliferation or transformation of a mammalian breast or ovarian cell *in vitro* or *in vivo*. It was general knowledge that a nucleotide sequence complementary to a coding sequence (sense strand) does not code for the same peptide or protein encoded by the coding sequence, or even does not code for any peptide or protein. The specification fails to provide adequate guidance and evidence for how to use the nucleotide sequence complementary to SEQ ID No. 10 or complementary to a degenerate coding sequence of SEQ ID No. 10 to inhibit neoplastic proliferation or transformation of a mammalian breast or ovarian cell *in vitro* or *in vivo*. Thus, one skilled in the art at the time of the invention would not know how to use the claimed nucleotide sequence and would require undue experimentation to practice over the full scope of the invention claimed.

The specification fails to provide adequate guidance and evidence that any expression vector comprising the polynucleotide set forth above can inhibit neoplastic cellular proliferation

or transformation of a mammalian breast or ovarian cell *in vivo* via any administration route other than direct *in situ* administration.

The claims read on gene therapy *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a

specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the lack of adequate guidance and evidence and the unpredictability in gene transfer as discussed above, one skilled in the art at the time of the invention would not know how to use various vectors comprising the polynucleotide encoding the amino acid sequence of SEQ ID No.

9 or its fragment containing the proline-rich region to inhibit neoplastic proliferation or transformation of a mammalian breast or ovarian cell via any administration route *in vivo*.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.